

Remarks

Upon entry of the foregoing amendment, claims 1-7, 10-12, 85-90, 92-97, 100-101, 115-121, 123-135 and 137-156 are pending in the application, with claims 1, 101, 138, 155 and 156 being the independent claims. Claims 90, 101 and 137, 138 and 139 are withdrawn from consideration. Claims 1, 6 and 155 are sought to be amended. New claim 156 is sought to be added. Claims 9, 91 and 122 are sought to be cancelled. Support for the amendment to claims 1 and 155 and new claim 156 may be found throughout the specification, *e.g.*, at p. 11-12, paragraph [0029], p. 19, paragraph [0049], p. 29, paragraph [0073], p. 34, paragraph [0088], p. 40, paragraph [0103], p. 18, paragraph [0048], p. 22-23, paragraph [0057], p. 77, paragraph [0196] and p. 15-16, paragraph [0038]. Entry and consideration of this amendment is respectfully requested.

Based on the above amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

At pages 2-3 of the Office Action, the Examiner rejected claim 6 for using the alleged trademark "primase." Applicant respectfully traverses this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicant has amended claim 6 to recite an RNA polymerase that is the product of dnaG gene. Applicants attach herewith a page from a molecular biology textbook that substantiates that "primase" is an enzyme that is the product of the dnaG

gene, and would be understood as such by a person of ordinary skill in the art. *See, e.g.*, Benjamin Lewin, *Genes V*, Oxford University Press, Oxford, 1995, p. 584 (**EXHIBIT A**).

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1-3, 6-10, 12, 85-87, 91, 92, 115-117, 120-123, 125-128, 135, 140-142, 144-147 and 151-156 under 35 U.S.C. § 102(b) as allegedly anticipated by Lu *et al.* (U.S. Patent No. 5,571,669)("Lu *et al.*"). The Examiner argues that while the invention does not appear to be drawn to that which is disclosed by the Lu *et al.*, the claims are broad and thus embrace embodiments which are anticipated by Lu *et al.* The Examiner contends that Lu *et al.* disclose a transcriptional sequencing method wherein the method comprises the steps of incubating a target polynucleotide with an RNA primer and extending the RNA primer/DNA template chimera with an RNA polymerase, wherein the method incorporates, during the transcription reaction, one or more nucleotide triphosphate analog reactants, wherein the analog reactants are explicitly contemplated as being a chain terminator. Applicant respectfully traverses this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 1 and 155 to more particularly point out that the claims are directed to, *inter alia*, an abortive transcription process wherein the initiator is a mononucleoside, mononucleotide, dinucleotide or trinucleotide or analog thereof, and the RNA polymerase transcribes the DNA in the context of a bubble complex.

In contrast, the method described by Lu *et al.* is a promoter-less primer extension reaction that utilizes primers of at least about 7 or more nucleotides in length. No bubble complex is formed in the context of the reaction described by Lu *et al.*, as is illustrated in Figure 4C of Lu *et al.* Moreover, the elongation complex of Lu *et al.* creates "increased yields of *fully extended transcripts and minimizes aborted RNA chains* . . ." See Abstract (emphasis added). The mechanism of primer extension of a single stranded target with an RNA polymerase, as taught by Lu *et al.*, is different than the claimed abortive transcription mediated by RNA polymerase and an initiator. Lu *et al.* disclose a primer extension reaction wherein the primer fully hybridizes to the template in the absence of a polymerase. The polymerase is then added to extend the primer. Lu *et al.* perform the reaction in this manner *to prevent an abortive reaction*. According to Lu *et al.*, primers at least about 7 or more nucleotides in length are necessary for elongation because "the limited interaction between nascent RNA chains <8 nucleotides and the template-enzyme complex may lead to failed elongation if these starting ternary complexes have a rate of dissociation that is comparable to or exceeds that of further elongation." See col. 10, lines 5-9.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 103

The first § 103 rejection

The Examiner has rejected claims 4, 5, 88, 89, 100, 118, 119 and 129 under 35 U.S.C. § 103(a) as allegedly obvious over Lu *et al.* in view of Sasaki *et al.* (*PNAS*,

95:3455-3460 (1998))("Sasaki *et al.*"). The gist of the Examiner's rejection is that, while Lu *et al.* do not disclose that fluorescent labels may be employed, Sasaki *et al.* disclose such labels and it would have been *prima facie* obvious to combine the teachings of Lu *et al.* and Sasaki *et al.* to arrive at the claimed invention. Applicant respectfully traverses this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 1 to more particularly point out that the claims are directed to, *inter alia*, an abortive transcription process wherein the initiator is a mononucleoside, mononucleotide, dinucleotide or trinucleotide or analog thereof, and the RNA polymerase transcribes the DNA in the context of a bubble complex.

As noted above, Lu *et al.* describe a promoter-less primer extension reaction that utilizes primers of at least about 7 or more nucleotides in length. No bubble complex is formed in the context of the reaction described by Lu *et al.*, as is illustrated in Figure 4C of Lu *et al.* Thus, whether it would be obvious to employ fluorescent labels is not material to the analysis.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The second § 103 rejection

The Examiner further rejected claims 11, 93, 94, 96, 97 and 124 as allegedly obvious over Lu *et al.* in view of Kramer *et al.* (U.S. Patent No. 5,503,979)("Kramer *et al.*"). According to the Examiner, while Lu *et al.* do not explicitly disclose that the

method comprises incubating the transcripts to a target site probe, or that a detection comprises hybridizing a complementary sequence to the synthesized transcripts, immobilizing the target sequence, or immobilizing by hybridization to a capture probe, Kramer *et al.* disclose a method of employing a capture probe to immobilize the target nucleic acid which would undergo further replication and it would be *prima facie* obvious to combine the teachings of Lu *et al.* and Kramer *et al.* Applicant respectfully traverses this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 1 to more particularly point out that the claims are directed to, *inter alia*, an abortive transcription process wherein the initiator is a mononucleoside, mononucleotide, dinucleotide or trinucleotide or analog thereof, and the RNA polymerase transcribes the DNA in the context of a bubble complex.

As noted above, Lu *et al.* describe a promoter-less primer extension reaction that utilizes primers of at least about 7 or more nucleotides in length. No bubble complex is formed in the context of the reaction described by Lu *et al.*, as is illustrated in Figure 4C of Lu *et al.* Thus, whether it would be obvious to incubate the transcripts to a target site probe, hybridize a complementary sequence to the synthesized transcripts for detection, or immobilize the target sequence to a capture probe, is not material, because neither Lu *et al.*, nor Kramer *et al.*, alone or in combination, disclose or suggest an abortive, reiterative method as claimed.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

The third § 103 rejection

The Examiner further rejected claim 95 as allegedly obvious over Lu *et al.* in view of Kramer *et al.* and further in view of Sasaki *et al.* The Examiner contends that while neither Lu *et al.* nor Kramer *et al.* disclose that fluorescent labels may be employed, Sasaki *et al.* disclose such labels and it would have been *prima facie* obvious to combine the teachings of Lu *et al.*, Kramer *et al.* and Sasaki *et al.* to arrive at the claimed invention. Applicant respectfully traverses this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 1 to more particularly point out that the claims are directed to, *inter alia*, an abortive transcription process wherein the initiator is a mononucleoside, mononucleotide, dinucleotide or trinucleotide or analog thereof, and the RNA polymerase transcribes the DNA in the context of a bubble complex.

As noted above, Lu *et al.* describe a promoter-less primer extension reaction that utilizes primers of at least about 7 or more nucleotides in length. No bubble complex is formed in the context of the reaction described by Lu *et al.*, as is illustrated in Figure 4C of Lu *et al.* Thus, whether it would be obvious to employ fluorescent labels is not material, because neither Lu *et al.*, Kramer *et al.* nor Sasaki *et al.*, alone or in combination, disclose or suggest an abortive, reiterative method as claimed.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

The fourth § 103 rejection

The Examiner further rejected claims 143 and 148-150 as allegedly obvious over Lu *et al.* in view of Gohara *et al.* (*Journal of Biological Chemistry*, 275:25523-25532 (2000))("Gohara *et al.*"). The Examiner contends that while Lu *et al.* do not explicitly disclose that the RNA-dependent RNA polymerase is a poliovirus RNA polymerase or that the target nucleic acid is from a virus, an RNA virus, or a bacterium, Gohara *et al.* disclose that poliovirus RNA polymerase utilizes DNA primers. The Examiner contends that it would have been *prima facie* obvious to employ any of the well known RNA polymerases in the method of Lu *et al.* as Lu *et al.* contemplate transcription of template nucleic acid via use of a DNA primer, and one of ordinary skill would have been motivated to employ any of the well known polymerases which acts on DNA primers for the purpose of transcriptional sequencing, with a reasonable expectation of success. The Examiner further contended that it would have been obvious to apply the teachings of Lu *et al.* for the purpose of detecting and characterizing the sequence of a virus or bacterium for the well established benefit of diagnosing infectious agents in patients and samples. Applicant respectfully traverses this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claim 1 to more particularly point out that the claims are directed to, *inter alia*, an abortive transcription process wherein the initiator is a mononucleoside, mononucleotide, dinucleotide or trinucleotide or analog thereof, and the RNA polymerase transcribes the DNA in the context of a bubble complex.

As noted above, Lu *et al.* describe a promoter-less primer extension reaction that utilizes primers of at least about 7 or more nucleotides in length. No bubble complex is

formed in the context of the reaction described by Lu *et al.*, as is illustrated in Figure 4C of Lu *et al.* Thus, whether it would be obvious to employ any of the well known RNA polymerases in the method of Lu *et al.*, or apply the teachings of Lu *et al.* for the purpose of detecting and characterizing the sequence of a virus or bacterium is not material, because neither Lu *et al.* nor Gohara *et al.*, either alone or in combination, disclose or suggest an abortive, reiterative method as claimed.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Obviousness-Type Double Patenting

The Examiner provisionally rejected, under the doctrine of obviousness-type double patenting, claims 1-12, 85-89, 91-97, 100, 115-136 and 140-156 over claims 11-17 and 19-27 of copending Application No. 10/425,037. The Examiner provisionally rejected, under the doctrine of obviousness-type double patenting, claims 1-12, 85-89, 91-97, 100, 115-136 and 140-150 (in part) over claims 136-147 of copending Application No. 10/686713. Applicant respectfully traverses this rejection.

Applicant respectfully requests that the Examiner hold the present provisional rejections in abeyance, pending the identification of otherwise allowable subject matter, at which time Applicant will consider filing any necessary terminal disclaimers.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the

Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Exhibit A

Figure 19.9

Priming requires several enzymatic activities, including helicases, single-strand binding proteins, a means of recognizing the primer assembly sequence, and other structural proteins.

dnaB
helicase (5'-3')
330,000 hexamer
~ 20 /cell

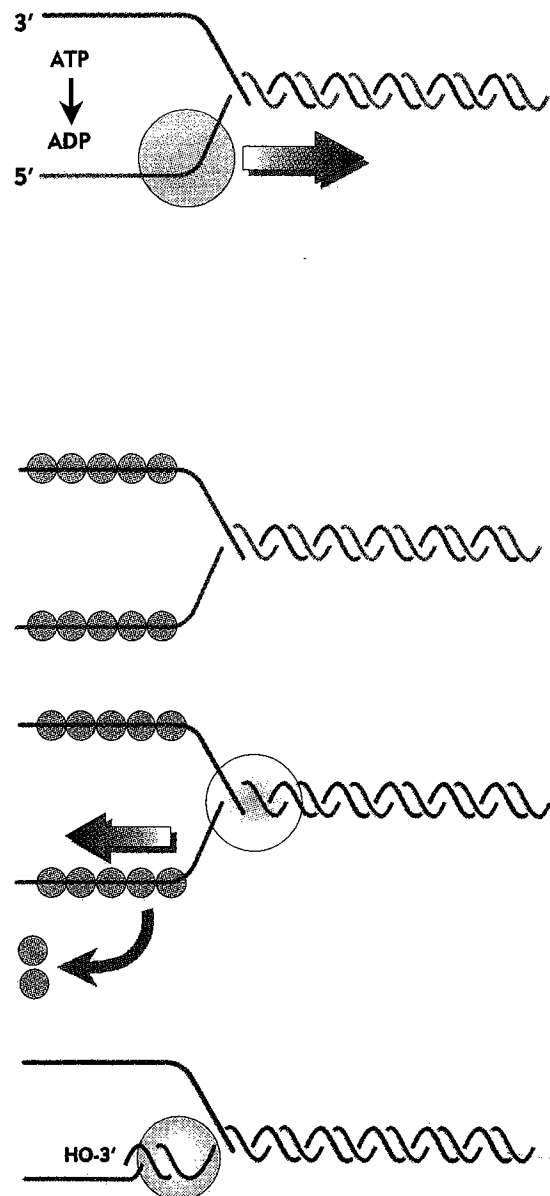
dnaC
acts with DnaB
29,000 monomer
(6 monomers /DnaB hexamer)
~ 20 /cell

dnaT
prepriming (1-2/fork)
66,000 trimer
~ 50 /cell

ssb
single-strand binding protein
76,000 tetramer
~ 200 /cell (60 /fork)

priA
recognizes primer assembly site
helicase (3'-5')
displaces SSB
82,000 monomer
~ 50 /cell (1/fork)

dnaG
primase synthesizes RNA
60,000 monomer
~ 75 /cell



The *pas* is recognized by PriA, which can displace SSB from single-stranded DNA. This may be important for allowing the primosome to assemble. PriA uses cleavage of ATP to provide energy for the reaction. The dual role of PriA as a helicase and in displacing SSB is unique to ϕ X primosomes, since PriA (and also PriB and PriC,

whose functions are unknown) is not required for replication of *oriC* primosomes.

The types of activities involved in the ϕ X174 priming reaction are summarized in Figure 19.9. Although other replicons in *E. coli* may have alternatives for some of these particular proteins, the same general

GENES V

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